

Retinal vascular features as a biomarker for psychiatric disorders

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CHAPTER 9

VALORISATION

Valorisation

Dealing with patients with psychosis and their caregivers who are struggling with their day to day activities is disheartening and emotionally draining for anybody. I encountered such a moment when I met one of my relatives, in his early teens, suffering from bipolar disorder. The grief and the burden which his parents had to carry on their shoulders triggered my interest to contribute to scientific research in this area. Considering the best outcome is seen when the treatment is initiated early, I decided to work on developing methods for early diagnosis so the treatment can be initiated at the earliest possible time.

Schizophrenia and Bipolar disorder, major psychotic disorders, are characterized by disturbances in cognition, perception, emotion, and motivation. Currently available treatment options reduce symptoms and suffering, however, there is no permanent cure. Mechanisms leading to psychosis are still unknown, which has hampered the development of curative interventions. The causes of psychosis are mostly a combination and interaction of genetic and environmental factors.

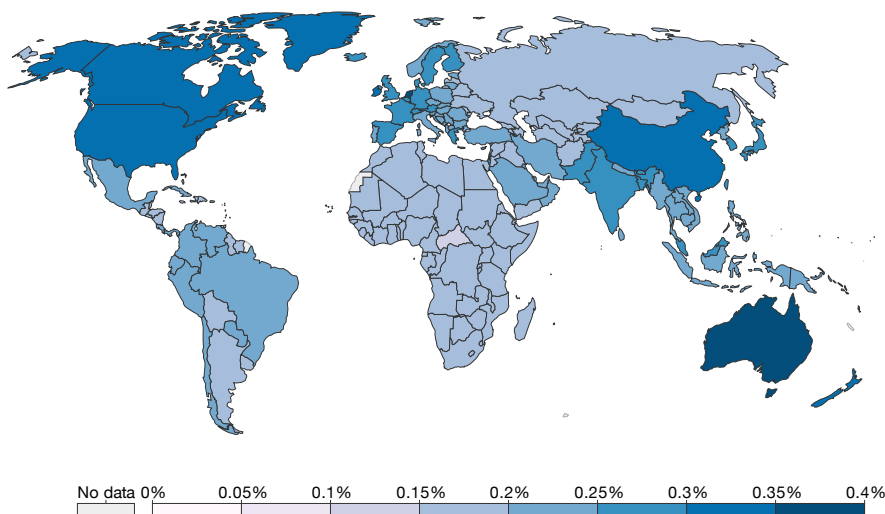
Clinically relevant symptoms of the psychosis spectrum have an estimated lifetime prevalence of 2.3% to 3.5% in the general population¹. They result in high social disabilities and costs to the society because of significant loss of productivity². Besides, societal stigmatization may result in a vicious cycle of discrimination leading to long-standing unemployment and social isolation, which further hinders the functional recovery. Therefore, early diagnosis and intervention are needed to lower the burden on patients with schizophrenia and bipolar disorder, their family members and furthermore, the society. Figure 1 depicts the share of worldwide population distribution for patients with schizophrenia and bipolar disorder.

Despite advances in the medical field, the diagnosis of psychosis is still dependent on the skill of the psychiatrist and hence involves the risk of subjective bias. Although psychiatric assessments have proven successful as a clinical tool for diagnosing psychosis, access to a trained mental health professional is difficult. This is especially true in developing countries including India (in particular the rural sector) where the doctor to patient ratio is very low and psychiatrists are hardly available. Even if a psychiatrist or a mental health professional is available, due to the subjective nature of the assessment, it may be erroneous at times.

Figure 1. Share of population with Schizophrenia and Bipolar disorder in 2017

Share of population with schizophrenia, 2017

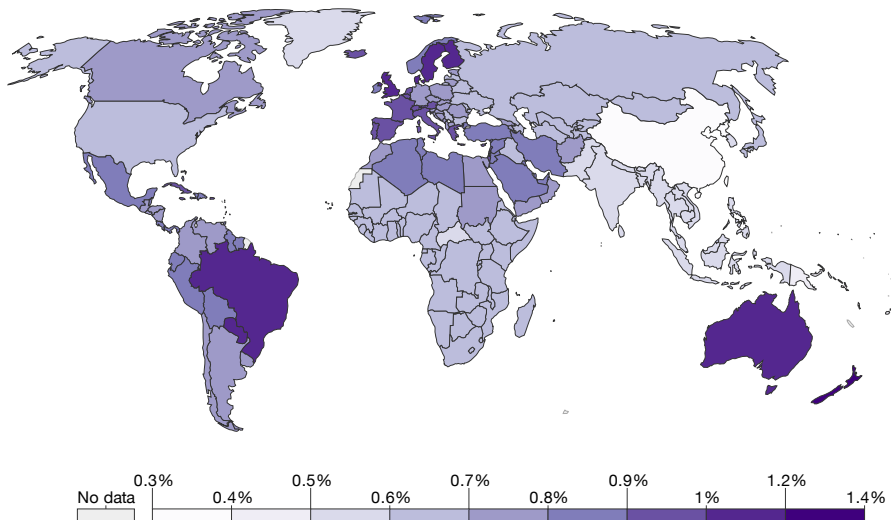
Share of the population suffering from schizophrenia. This share has been age-standardized assuming a constant age structure to compare prevalence between countries and through time. Figures attempt to provide a true estimate (going beyond reported diagnosis) of schizophrenia prevalence based on medical, epidemiological data, surveys and meta-regression modelling.



Source: IHME, Global Burden of Disease

Share of population with bipolar disorder, 2017

Share of the population with bipolar disorder. This share has been age-standardized assuming a constant age structure to compare prevalence between countries and through time. Figures attempt to provide a true estimate (going beyond reported diagnosis) of bipolar disorder prevalence based on medical, epidemiological data, surveys and meta-regression modelling.



Source: IHME, Global Burden of Disease

Currently, there is no definitive, quantitative assessment or specific biomarker which can help in the screening or confirmation of the diagnosis of psychiatric disorders. Absence of a biomarker and lack of necessary skill sets among the general practitioners prevents early diagnosis of individuals with psychosis or those who are at risk of development of psychosis. This often leads to undue delay in initiating prompt intervention, not only in resource-constrained societies, but also in urban areas. Hence, there is a requirement of a quantitative biomarker that can help in the early diagnosis of psychiatric disorders and serve as a screening tool for necessary referrals. This biomarker should be easily accessible, non-invasive and affordable to be utilised as a community screening tool.

While several candidate biomarkers are being examined, magnetic resonance imaging (MRI) is well evaluated as it is non-invasive. MRI is a sophisticated modality which allows the physician to visualize the structural, functional and chemical abnormality in the brain. MRI is routinely used as an investigation to examine brain abnormalities in neurological disorders. Several MRI studies have reported structural and functional brain abnormalities in schizophrenia and bipolar disorder, however its utility in routine clinical practice to diagnose psychosis is not well established. Even though MRI is found to be useful as a clinical tool in the diagnostic work up of psychosis, it is neither easily accessible nor affordable. This is notable in developing countries, including India, where only a handful of hospitals and advanced diagnostic centres have the facilities for brain imaging. Rural communities have no access to these facilities and are forced to travel to metropolitan cities for these investigations. Even in places where it is available, it is not as affordable.

Hence, several affordable and portable tools which are proxy markers of brain abnormalities are examined as potential biomarkers. Retinal fundus imaging presented in this thesis is an inexpensive, portable and easily accessible technology which has the potential to help in the early detection of psychosis. The cost-effectiveness, portability and easy accessibility makes retinal fundus imaging an ideal candidate that can be used even in primary and rural healthcare centres. Also, the non-invasive nature of retinal imaging used in this thesis gives an edge for usage in the wider community and paves the way for faster adaptability throughout the society. It is also objective, repeatable and has the potential to be utilized in community mass screening. The screening can be done by non-clinical personnel, as one needs minimal training to use the device. The imaging is non-mydratic and does not require any kind of dilator. This makes the imaging even easier and does not affect patient's work for the entire day.

It has been validated and published in this thesis that features from retinal fundus imaging are significantly different in patients with psychiatric disorders versus healthy volunteers. When compared to healthy volunteers (HV), schizophrenia (SCZ) and bipolar disorder (BD) patients had wider veins and narrower arteries (chapter 2). The retinal arteriolar tortuosity index was found to be higher in patients with SCZ and BD when compared to HV (chapter 3), and the results were similar for fractal dimensions (chapter 4). The retinal vascular trajectories were smaller in patients with SCZ and BD when compared to HV in both arterioles and venules (chapter 5).

In addition, as an exploratory analysis, machine learning using a supervised ensemble of bagged trees, was implemented to check if retinal vascular trajectories can be a potential utility as a predictive biomarker. It had an accuracy of 86% with a sensitivity of 88% and a specificity of 85% for differentiating HV and SCZ. However, a lower but considerably good accuracy of 73% with a sensitivity of 78% and a specificity of 76% was obtained for differentiating HV and BD (chapter 5). These findings of machine learning analysis suggested that the automated analysis using retinal vascular trajectory can classify diagnosed patients and healthy volunteers with reasonable accuracy. Hence, retinal vascular trajectory is a potential biomarker for SCZ and BD. In addition to these structural features, the retinal vascular abnormalities were related to cognitive deficits typically seen in SCZ and BD. There was a significant association between working memory deficits, narrower arterioles and wider venules; a significant positive correlation between one-back test accuracy and retinal arteriolar calibre as well as significant positive correlation between log mean speed score and retinal venular calibre (chapter 6).

The machine learning algorithms were implemented using retinal vascular trajectories as features. However, it can be further explored to combine the other features including calibre, tortuosity and fractal dimensions. A combination of measures may provide a higher accuracy when compared to single measure. The machine learning algorithms can be packaged into the software which can be used across operating systems and aid in classifying or identifying the psychosis. The images can be acquired using the existing portable fundus camera or a mobile-based fundus camera in the future. The minimal computational requirement of the machine learning algorithms used in this thesis allows the algorithm to be used in a cloud based analysis and classification so it can be used in resource constrained settings.

One of the main objectives of this thesis was to cater to the societies in lower- and middle-income countries that do not have easy access to healthcare - especially mental health. It is important to address this issue as the loss of productivity and the burden caused to the caregivers as well as the society due to psychosis is increasing every day due to lack of early diagnosis and prompt intervention. It is also seen that neurobiological changes occur earlier than the development of clinical symptoms. Unfortunately, the psychosis is diagnosed only in advanced stage after the clinical symptoms are more prominent and treatment is started subsequently. The reasons for delay in treatment is due to the absence of tools for early diagnosis and inaccessibility of experts. Hence, this novel method using retinal imaging may help in early diagnosis which will result in early medical intervention. This will also improve the patient's functional recovery and decrease the economic and emotional burden on family and society.

From the present thesis, it can be concluded that retinal vascular abnormalities are present in schizophrenia and bipolar disorder. Fundus imaging may pave the way to novel screening / diagnostic tools and indirectly help in early interventions. Nevertheless, much work is needed before retinal imaging can be used routinely in the clinical setting. Advances in, and direct comparisons of the various analysis methods are to be further tested. While the accuracy of the machine learning analysis was tested in a group level in the present thesis, the efficiency of the tool has to be tested at an individual level for its clinical utility.

The research presented in this thesis would be of interest to the governments of developing countries like India where there is an immediate need to have accessible, inexpensive screening tools for mental health conditions. In the rural community without access to specialists and advanced investigations, retinal fundus imaging may potentially be used to screen for mental disorders. As retinal fundus imaging can be acquired easily, this tool can be employed by general medical practitioners thus increasing its utility in wider community.

Before it can be used in the community or in the clinical setting, it is important to completely validate the research presented in this thesis by correlating the retinal vascular features with the brain vascular abnormalities using well-proven techniques like Arterial Spin Labelling (ASL). This thesis is presented with 100 sample size in each patient group when compared to 100 HV. However, the results have to be replicated with wider populations to have scientific validity. Further longitudinal follow-up

studies will also help in identifying the stage of illness and predicting individuals who are at risk of developing the illness.

Even though the identification of group differences has improved our knowledge, it is necessary to show the difference at an individual level for the tool to be clinically useful. This thesis has paved the way for future individualistic classification. One possible approach is to generate single-subject inferences through machine learning classifiers^{3,4} using retinal vascular features. To arrive at definite conclusions about retinal vascular abnormalities associated with schizophrenia or bipolar disorder, one should replicate this finding from a different geographical location. The present work was conducted at a tertiary health care centre - the National Institute of Mental Health and Neurosciences, Bengaluru, India. Future works in primary and secondary care centres need to be conducted for generalizability of the findings. Subsequently, population-based studies are needed for application as a screening tool in community.

Translating this academic research into an economically sustainable screening and diagnosis program will provide real-life application. Hopefully the results of this thesis will inspire indigenous biomedical device companies in India to investigate further in creating a low-cost screening device that embeds the algorithms of this thesis as an application available with the device. One of the major challenges in using MRI for screening is the cost and the portability of the neuroimaging equipment. If the local products can fill this gap, by integrating the low-cost screening devices with this algorithm, they may increase the outreach of the tool. This Ph.D. research will open doors for replication studies with larger sample size and longitudinal studies. Further clinical validation of such devices would create a global market for the same. Smart-phone apps can be developed for analysis and visualization of the patient data which can be available for the technicians, experts and paramedics.

Within the scientific community, knowledge dissemination is done through publications in peer-reviewed journals and presentations at research conferences and other scientific forums. A part of the thesis was presented in the World Bipolar Day Conference on 24 March 2019 at NIMHANS, Bengaluru, India. The conference was attended by clinicians, mental health professionals and researchers across India. Several researchers expressed interest to collaborate further for the research and clinical validation. Research results and methodological developments can be further discussed with other scientists, driving international collaboration and brainstorming on analytic approaches. This thesis was implemented in a developing country (India)

in collaboration with the Netherlands, but the concepts and the methodology can be further expanded to other countries and may become a model of reverse innovation.

This research has already been explored beyond the thesis chapters. Along with one of my co-supervisors, Dr. Naren P. Rao, we had submitted a research proposal to assess the retinal vascular abnormalities in first degree relatives of patients with schizophrenia. This research will provide the necessary next step to establish the potential of this method to identify at risk individuals and whether these abnormalities are endophenotypes. The research project is approved for funding by the Department of Science and Technology (DST), Government of India under Cognitive Science Research Initiative (CSRI). We are in the process of taking necessary permissions from institute ethics committee to start the project. Another proposal is under development to design a hyperspectral device that can give dynamic vessel analysis and oxygen saturation of retinal images which can further help to strengthen the concepts presented in this thesis.

Clinically, retinal fundus imaging is considered as a relatively affordable, accessible and workable tool for screening the patients. Hence, it is our hope that the efforts laid out in this thesis represent a small step in the global effort to improve the lives of patients with schizophrenia and bipolar disorder.

Thus I would like to conclude with a quote “***Medicine is a science of uncertainty and an art of probability***” - Sir William Osler, a Canadian physician and one of the founding professors of Johns Hopkins Hospital, USA.

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